INVESTIGATIONAL PLAN

PROTOCOL

1.0 GENERAL INFORMATION

1.1 Introduction

This clinical trial is being conducted to evaluate the rhBMP-2/CRM/CD HORIZON® Spinal System for posterolateral fusion treatment of patients with symptomatic degenerative disc disease versus the control group of autogeneous bone with the CD HORIZON® Spinal System. The study will involve a total of up to 480 patients at no more than thirty sites, with all centers following a common Clinical Investigational Plan (CIP). It is anticipated that the data from this clinical trial will be used to support regulatory approval to commercialize the implant.

1.2 Investigational Implant

The rhBMP-2/CRM component of the investigational device consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) and a compression resistant matrix (CRM) carrier consisting of an absorbable collagen sponge imbedded with biphasic calcium phosphate.

BMP-2 is a natural human protein that has been shown in animal studies to induce bone formation. The human BMP-2 protein sequence has been cloned and expressed in mammalian cells to yield large quantities of highly purified rhBMP-2 (Wozney, 1988).

The carrier component, the CRM, provides the matrix for the delivery of rhBMP-2 and serves as a temporary space-filler at the surgical site. The CRM consists of an absorbable collagen sponge (from Integra LifeSciences) with resorbable biphasic calcium phosphate granules imbedded into the sponge, which is placed across two adjacent

transverse processes. The resorbable biphasic calcium phosphate consists of 15% Hydroxyapatite and 85% Tricalcium Phosphate (HA/TCP).

The posterior spinal fixation system, the CD HORIZON® Spinal System, is a commercially available rod-based spinal system intended for temporary stabilization of the spine in order to facilitate fusion. The CD HORIZON® Spinal System is available in either titanium or stainless steel. For this study, only titanium implant components will be used.

1.3 Control Implant

The control will be autogenous bone taken from the iliac crest of the patient and placed bilaterally across two adjacent transverse processes and used in conjunction with the CD HORIZON® Spinal System. When used as a posterior spine thoracic/lumbar system, the CD HORIZON® CANNULATED M8 MULTI-AXIAL SCREW components are intended for several indications including degenerative disc disease.

2.0 PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of this clinical trial (rhBMP-2/CRM/CD HORIZON® Spinal System) is to evaluate the implant as a method of facilitating spinal fusion inpatients with degenerative disc disease. It is anticipated that the data from this clinical trial will be used to support regulatory approval to commercialize the implant.

This system is indicated for one level, posterolateral lumbar fusion in patients with degenerative disc disease. Degenerative disc disease (DDD)

is defined as back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history (e.g., pain [leg, back, or symptoms in the sciatic nerve distribution], function deficit and/or neurological deficit) and radiographic studies (e.g., CT, MRI, X-Ray, etc.) to include one or more of the following:

(a) instability (defined as angular motion $\geq$ 5° and/or translation $\geq$ 4 mm, based on Flex/Ext radiographs);

(b) osteophyte formation;

(c) decreased disc height;

(d) thickening of ligamentous tissue;

(e) disc degeneration or herniation; and/or

(f) facet joint degeneration.

2.2 Primary Objective

Overall Success

The primary objective of this clinical trial is to evaluate the overall success rate associated with the use of the investigational implant. Overall success will be the primary clinical trial endpoint. Overall success is defined in Section 5.1 of this protocol and the parameter includes the primary safety and effectiveness considerations for the investigational and control products. If the overall success rate for the investigational treatment is statistically equivalent to, i.e., no worse than, the overall success rate for the control group at 12 months following surgery, the investigational implant will be considered to be safe and effective. Please refer to the Statistical Considerations section of the Investigational Plan for additional information.

2.3 Secondary Objectives

Secondary objectives of this clinical trial will be to compare the success rates of the individual safety and effectiveness endpoints, including operative measurements.

The comparisons will be to determine statistically if equivalence between the investigational and control treatments exist. If the investigational treatment is found to be statistically equivalent to, i.e., no worse than, the control treatment, superiority of the investigational treatment to the control will also be evaluated. In addition, superiority analyses will be performed for the overall success parameter if equivalence has been demonstrated. Please refer to the Statistical Considerations section of the Investigational Plan for additional information regarding secondary objectives.

3.0 STUDY DESIGN

3.1 Description

This clinical trial has a multi-center, prospective, randomized, controlled design. Patients and surgeons will not be blinded to the surgical treatment. The independent radiologists who evaluate the radiographs and CT scans will not be informed of the treatment.

3.2 Treatment Groups

The investigational treatment is the open bilateral posterolateral implantation of the rhBMP-2/CRM/CD HORIZON® Spinal System. One investigational implant is placed across two adjacent transverse processes on each side of the spine during the spinal fusion procedure. The control treatment is the bilateral posterolateral implantation of the

autogenous bone harvested from the iliac crest with the CD HORIZON® Spinal System. The guidelines for surgical implantation of these implants are located in the Surgical Technique section.

3.3 Sample Size

This study will enroll a total of up to 480 (±10) patients with an estimated 240 Investigational and 240 Control patients. These patients will be enrolled at no more than 30 investigational sites. Each investigational site will have a 1:1 investigational control treatment randomization scheme. It is estimated that enrollment will take 12 months.

4.0 PATIENT POPULATION

4.1 Patient Eligibility Criteria

Prospective patients will have been diagnosed with degenerative disc disease with an option for treatment being a lumbar fusion procedure. Patients must be geographically stable and able to attend follow-up examinations at the investigational site. Patients are expected to have long-term participation (approximately 2-4 years) in the clinical study. In addition, all patients must agree to undergo the necessary preoperative and postoperative evaluations specified in this CIP.

4.2 Inclusion Criteria:

Each patient participating in this clinical trial must meet **all** of the following inclusion criteria:

a. Has degenerative disc disease as noted by back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed

by patient history (e.g., pain [leg, back, or symptoms in the sciatic nerve distribution], functional deficit and/or neurological deficit) and radiographic studies (e.g., CT, MRI, X-Ray, etc.) to include one or more of the following:

(a) instability (defined as angulation $\geq$ 5° and/or translation $\geq$ 4mm, based on flexion/extension radiographs);
(b) osteophyte formation;
(c) decreased disc height;
(d) thickening of ligamentous tissue;
(e) disc degeneration or herniation; and/or
(f) facet joint degeneration.

2. Has preoperative Oswestry score $\geq$ 30.
3. Has no greater than Grade 1 spondylolisthesis utilizing Meyerding's Classification (Meyerding, HW, 1932).
4. Requires fusion of a single level disc space from L1 to S1.
5. Is at least 18 years of age, inclusive, at the time of surgery.
6. Has not responded to non-operative treatment (e.g., bed rest, physical therapy, medications, spinal injections, manipulation, and/or TENS) for a period of 6 months.
7. If of child-bearing potential, patient is non-pregnant, non-nursing, and agrees to use adequate contraception for 1 year following surgery.
8. Is willing and able to comply with the study plan and sign the Patient Informed Consent Form.

4.3 Exclusion Criteria:

A patient meeting **any** of the following criteria is to be **excluded** from this clinical trial:

1. Has primary diagnosis of a spinal disorder other than degenerative

disc disease with Grade 1 or less spondylolisthesis at the involved level.

2. Had previous spinal fusion surgical procedure at the involved level.
3. Requires spinal fusion at more than one lumbar level.
4. Has a condition which requires postoperative meditations that interfere with fusion, such as steroids or prolonged use of nonsteroidal anti-inflammatory drugs excluding routine peri-operative nonsteroidal anti-inflammatory drugs. This does not include low dose aspirin for prophylactic anticoagulation.
5. Has been previously diagnosed with osteopenia or osteomalacia.
6. Has any of the following that may be associated with diagnosis of osteoporosis (if "Yes" to any of the below risk factors, a dual x-ray absorptiometry (DEXA) Scan will be required to determine eligibility.)
   a. Postmenopausal Non-Black female over 60 years of age and weighs less than 140 pounds.
   b. Postmenopausal female that has sustained a non-traumatic hip, spine, or wrist fracture.
   c. Male over the age of 70.
   d. Male over the age of 60 that has sustained a non-traumatic hip or spine fracture.

   If the level of BMD is a T score of -3.5 or a T score of -2.5 with vertebral crush fracture, then the patient is excluded from the study.
7. Has presence of active malignancy or prior history of malignancy (except for basal cell carcinoma of the skin).
8. Has overt or active bacterial infection, either local or systemic.
9. Has a documented titanium alloy allergy or intolerance.
10. Is mentally incompetent. If questionable, obtain psychiatric consult.

11. Has a 'Waddell Signs of Inorganic Behavior' score of 3 or greater.
12. Is a prisoner.
13. Is an alcohol and/or drug abuser as defined by currently undergoing treatment for alcohol and/or drug abuse.
14. Has received drugs which may interfere with bone metabolism within two weeks prior to the planned date of spinal fusion surgery (e.g., steroids or methotrexate).
15. Has a history of autoimmune disease (e.g. Systemic Lupus Erythematosus or dermatomyositis).
16. Has a history of exposure to injectable collagen or silicone implants.
17. Has a history of hypersensitivity to protein pharmaceuticals (monoclonal antibodies or gamma globulins) or collagen.
18. Has received treatment with an investigational therapy within 28 days prior to implantation surgery or such treatment is planned during the 16 weeks following rhBMP-2/CRM implantation.
19. Has received any previous exposure to any/all BMP's of either human or animal extraction.
20. Has a history of allergy to bovine products or a history of anaphylaxis.
21. Has history of endocrine or metabolic disorder known to affect osteogenesis (e.g., Paget's disease, renal osteodystrophy, Ehlers-Danlos syndrome, or osteogenesis imperfecta).

5.0 MEASUREMENTS

The outcome criteria outlined in this section will be used to evaluate the patient's postoperative treatment.

5.1 Overall Success

A patient will be considered an overall success if all of the following conditions are met (specific conditions for these parameters are defined in subsequent sections of the protocol):

1. fusion;
2. pain/disability (Oswestry) improvement;
3. maintenance or improvement in neurological status;
4. no serious adverse event classified as implant associated or implant/surgical procedure associated;
5. no additional surgical procedure classified as a "failure."

5.2 Safety

5.2.1 Adverse Events

The criteria outlined in this section will be used to evaluate each patient during surgery and postoperatively to determine the safety associated with the patient's treatment. The safety of the investigational and control treatments will be assessed by comparing the nature and frequency of adverse events.

An adverse event (AE) means any clinically adverse sign, symptom, syndrome, or illness that occurs or worsens during the operative and postoperative periods of the trial, regardless of causality, that is not being measured otherwise in the trial. This does not necessarily include immediate post-operative sequelae such as chills, sore throat, nausea, vomiting, constipation, short-term fever unrelated to infection, straight catherization, pain or burning during urination, etc., unless it prolongs hospitalization or in the opinion of the investigator should be reported. Each adverse event will be evaluated in light of its severity, association with the

implant, and whether it resulted in a second surgical procedure. These considerations are further defined as follows:

1. Severity

The severity of adverse events will be assessed according to the World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects (see WHO Grading Section).

The following definitions should be used for events that are not defined in the WHO Toxicity Scale:

- Mild (Grade 1): The adverse event is noticeable to the patient but does not interfere with routine activity. The adverse event does not require removal of the implant.
- Moderate (Grade 2): The adverse event interferes with routine activity but responds to symptomatic therapy or rest. The adverse event does not require removal of the implant.
- Severe (Grade 3): The adverse event significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the adverse event may require removal of the implant.
- Life-threatening (Grade 4): The adverse event requires removal of the implant. The patient is at immediate risk of death.

2. Association with Implant

The relation between an adverse event and the implant will be assessed on the basis of the following definitions:

- Implant Associated: There is a reasonable possibility that the adverse event may have been caused by the implant(s).
- Surgical Procedure Associated: There is a reasonable possibility that the adverse event may have been caused primarily by the surgical procedure.
- Implant/Surgical Procedure Associated: There is a reasonable possibility that the adverse event may have been caused by both the implant and the surgical procedure.
- Undetermined (Unknown): Sufficient information is not available at the time of the event to determine its causality.
- Not Related: An adverse event for which sufficient information exists to indicate that the etiology is unrelated to the implant(s) or surgical procedure.

5.2.2. Secondary Surgical Procedure

Some adverse events or treatment failures may lead to additional surgical intervention. These surgical interventions will be classified as follows:

Revision: A procedure that adjusts or in any way modifies the original implant configuration (e.g., adjusting position of the original configuration, removal with replacement with the same type of trial implant).

Removal: A procedure that removes one or more components of the original implant configuration without replacement with the same type of trial implant. **NOTE: In the event that an implant requires non-elective removal, please refer to the attached Explanted Implant section for instructions and information.**

Removals will be classified as either elective or non-elective. An elective removal is a procedure that removes the temporary implant system, the CD HORIZON® Spinal System, after the development of fusion and at the discretion of the investigator and/or patient. An elective removal is not the result of an adverse event or pseudarthrosis. Possible reasons for elective removals are as follows:

1) Patient Preference

- Cosmetic reasons, i.e., prominent hardware;
- Psychological reasons;

2) Surgeon Preference

- Convenient removal in the presence of fusion during additional spinal surgery at a different level;
- Removal in the presence of fusion to facilitate an additional spinal surgery.

Supplemental Fixation: a procedure in which additional spinal implants not approved as part of the protocol are placed. This may include supplemental placement of an interbody fusion device. In addition, an uninstrumented posterior or posterolateral fusion surgical intervention will be classified as a supplemental fixation.

Reoperation: A procedure that involves any surgical procedure at the involved level that is not a Removal, Revision and Supplemental Fixation.

Other: Any additional surgical procedure not classified as a Removal, Revision, Supplemental Fixation, or Reoperation.

A supplemental fixation, non-elective implant removal, or revision will be classified as a treatment "failure." A reoperation, elective removal, or other surgical procedure will not be classified as a treatment "failure." All patients having secondary surgical procedures will be followed for the duration of the study for safety. The rates of secondary surgical procedures for the two treatment groups will be compared.

All adverse events will be reported on Adverse Event Case Report Forms and each will be classified according to the aforementioned criteria. The frequencies of the categorized adverse events in each treatment group will be compared.

5.2.3 Neurological Status

Neurological status will be assessed preoperatively and postoperatively using a neurological status scale. Neurological status is based on four types of measurements (sections): motor, sensory, reflexes, and straight leg raise.

The method for summarizing the neurological findings is as follows. A score for each parameter, i.e., motor, sensory, reflexes, or straight leg raise, will be calculated. If "normal" is indicated for a parameter, the score is assigned as "100".

If a parameter is assessed as "abnormal", its components are evaluated and developed into scores as follows:

Sensory: Sum component scores.

Code score dichotomously as follows:

1 If Normal

0 If Absent or Impaired

The maximum possible score is 24.

Motor: Sum component scores.

Code score dichotomously as follows:

1 If Active Movement against Full Resistance

0 If Total Paralysis, Palpable or Visible Contraction, Active Movement Gravity Eliminated, Active Movement against Gravity, Active Movement against Some Resistance

The maximum possible score is 10.

Reflexes: Sum component scores.

Code score dichotomously as follows:

1 If Normal or Hypo-reflexic

0 If Absent or Trace, Hyperreflexic

The maximum possible score is 4.

Straight Leg Raise: Sum component scores.

Code score dichotomously as follows:

1 if Normal

0 If Abnormal

The maximum possible score is 4.

If a question(s) is not answered, the maximum score for that particular parameter is reduced accordingly. For example, if only 8 of the 10 motor questions are answered, i.e., two responses are missing, the maximum possible score is 8.

Each parameter score is then converted to a percentage using the following equation:

$$\text{Score (\%)} = \frac{\text{Total X 100\%}}{\text{Maximum}}$$

Thus an "abnormal" parameter will have a score less than 100, as compared with 100 for a normal parameter.

The postoperative scores of the parameters are compared to the preoperative scores. A successful outcome will be declared for that parameter if Postoperative Score - Preoperative Score $\geq$ 0. If a preoperative parameter score is missing, the postoperative status

will be considered a success if the postoperative score is 100; a failure if the postoperative score is 0; and missing if otherwise. Overall measure of neurological status will be based on success statuses in the four parameters. The overall neurological status will be deemed a success if, and only if, all the four parameters are successes. If any one of the parameters is a "failure", the overall neurological status is a "failure". Otherwise, if one or more parameters are missing, the overall neurological status is treated as missing.

5.2.4 Unanticipated Adverse Device Event

An unanticipated adverse device event is 'any serious adverse event on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, . . .or any other unanticipated serious problem associated with a device that relates to the rights, safety, and welfare of subjects."[1] An investigator in this clinical trial must report any unanticipated adverse device event to Medtronic Sofamor Danek and his/her IRB within 10 working days of the occurrence.

5.3 Effectiveness

The outcome criteria outlined in this section will be used to evaluate each patient postoperatively to determine if the patient's treatment is considered effective. The data for the investigational group will then be compared to those in the control group. In addition, treatment group comparisons may be made based on

[1] 21 CFR 812.3(s).

actual measurement or changes over time, e.g. treatment group comparisons of Oswestry scores or changes in Oswestry scores.

5.3.1 Primary Effectiveness Endpoints[2]

5.3.1.1 Fusion

Fusion is defined as:

- Evidence of bridging trabecular bone. This is based on the evidence of a continuous bony connection from the superior transverse process to the inferior transverse process.

  Method — Radiographs

  If evidence of bridging trabecular bone cannot be observed with radiographs, CT scans (see CT Imaging Protocol section) will be used as a secondary method only of observing bridging trabecular bone;

  - No evidence of motion as defined by:
    a. No more than 3mm difference in translation on the lateral flexion/extension radiographs as determined by superimposing the two views, one upon the other.
    b. Less than 5° difference in angular motion between flexion and extension as seen on lateral flexion/extension radiographs

       Method - Flexion/Extension radiographs*;

  - Absence of cracking, as evidenced by radiolucent lines completely through the fusion mass.

[2] A primary effectiveness endpoint is one that is included in the overall success parameter.

Method - radiographs.

*Do not rotate hips on flexion/extension radiographs.

All of these criteria must be met to be classified as fused. The radiographic review will be completed by two independent radiologists and reported on the Radiographic Review case report form. If there is a disagreement regarding the ultimate fusion status of the patient between the two radiologists, a third independent, blinded radiologist will be used to break the tie.

5.3.1.2 Pain/Disability Status

The self-administered Oswestry Low Back Pain Disability Questionnaire (McDowell, I, *et al.,* 1996) will be used. Success will be defined as pain/disability improvement postoperatively according to the following definition:

Preoperative Score - Postoperative Score $\geq$ 15 points

5.3.2 Secondary Effectiveness Endpoints

5.3.2.1 General Health Status

The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) (Ware, JE, *et al.*, 1994) will be used to assess general health status. The SF-36 results, which are regarded by FDA as a measure of patient satisfaction and quality of life, can be summarized into two components, a physical component summary (PCS) and a mental component summary (MCS) according to

algorithms formulated by the Medical Outcomes Trust, the developers of the SF-36 survey.

Success will be defined as a maintenance or improvement in status postoperatively as compared to the preoperative condition. To be classified as a success, the following criteria must be met:

$$PCS_{Postop} - PCS_{Preop} \geq 0$$

$$MCS_{Postop} - MCS_{Preop} \geq 0$$

5.3.2.2 Pain Status

Back Pain Status

Numerical rating scales, adapted in part from Measuring Health (McDowell I, *et al.* Newell, 1996), will be used to evaluate back pain. Back pain score is the summation of pain intensity and duration scores measured on the numerical rating scales.

Success for back pain according to this measurement method is described as follows:

Preoperative Score - Postoperative Score ≥ 0
(Score = pain intensity + pain duration)

Treatment group comparisons may be made based on actual measurements or changes in measurements from preoperative to postoperative scores.

Leg Pain Status

Numerical rating scales as described above will also be used to measure leg pain. Success is predicated on an improvement in leg pain status according to the following equation:

$$\text{Preoperative Score} - \text{Postoperative Score} \geq 0$$
(Score = pain intensity + pain duration)

Treatment group comparisons may be made based on actual measurements or changes in measurements from preoperative to postoperative scores.

5.3.2.3 Patient Satisfaction

Patient satisfaction questions will be administered postoperatively. Three questions will be asked and they will be evaluated separately. Success for each question will be defined as either a "Definitely True" or "Mostly True" response. The treatment group results will be compared.

5.3.2.4 Patient Global Perceived Effect

Postoperatively, the patient will be asked a question regarding the perceived effect of his/her surgical treatment. Success will be defined as either a "Completely Recovered," "Much Improved," or "Slightly Improved" response. The treatment group results will be compared.

5.4 Other Measurements

5.4.1 Antibody Monitoring

rhBMP-2 and bovine collagen antibody screening will be performed on each patient, both investigational and control. Blood samples will be drawn preoperatively and at 6 weeks, 3 months, 6 months, and 12 months postoperatively for this purpose. Alta-Labs (San Diego, California) will perform the assays. If the bovine collagen antibody level is found to be positive, human Type I collagen antibody assay testing will also be performed. Additional samples may be necessary if authentic positive antibodies are seen and/or samples cannot be reliably tested. The procedure for these serum sample collections is detailed in Attachment IV.A.6, entitled Serum Collection.

The results of patients exhibiting authentic positive antibodies will be evaluated and compared to the results of those patients not exhibiting authentic positive antibodies. This will include an evaluation of adverse event(s) in patients having authentic positive antibody results.

5.4.2. Hip (Donor Site) Pain Status

Control group patients will have bone graft harvested from their iliac crests. The level of postoperative pain and morbidity associated with the graft harvest procedure will be measured using numerical rating scales. One of the expected benefits of the investigational implant is that bone graft harvesting is not necessary and any pain associated with it will be precluded.

5.5 Measurement Times

Data for all patients entered into the study will be collected on case report forms at the following timepoints:

1. Preoperative – Data obtained within six months prior to surgery.
2. Surgery and Hospital Discharge - Data obtained during surgery and prior to hospital discharge.
3. Postoperative - Data obtained postoperatively at 6 weeks ± two weeks, 3 months ± two weeks, 6 months ± 1 month, 12 months ± 2 months, and 24 months ± 2 months, and annually thereafter until the last patient entered into the study has completed his/her evaluation at the 24 month mark.

Investigational sites are requested to notify the sponsor of intended use of the implant prior to the surgery. This may occur via telephone or facsimile.

All appropriate sections of the case report forms (CRFs) must be filled out completely and accurately in black ink. Prior to submission of CRFs, the forms should be reviewed for accuracy. The case report forms are faxed to Medtronic Sofamor Danek with the original and copy remaining at the investigational site in the patient's case report form book. Original CRFs may be collected from the site after records have been monitored. **CRFs should be submitted to the sponsor within 6 weeks of the examination.**

Data corrections to the CRFs by the investigational site should be made in black ink. A single line should be drawn through the incorrect data and corrections should be documented with the date and initials of the individual making the change. The use of correction fluids or obliteration of data is not permitted.

The following table indicates the information, case report forms and radiographic procedures to be completed at the various study intervals:

			Postoperative				
Procedure	**Preoperative**	**Surgery/ Hospital Discharge**	**6 wks ±2 wks**	**3 mo. ±2 wks**	**6 mo. ± 1 mo.**	**12 mo. ± 2 mo.**	**24 mo. ± 2 mo. & annually**
Preoperative Information							
Confirm patient eligibility	X						
Obtain Informed Consent	X						
Open randomization envelope	X						
Case Report Forms							
Patient Enrollment	X						
Patient Qualification Form	X						
Preoperative Data	X						
Preoperative Patient Survey	X						
Preoperative Oswestry	X						
Blood Specimens for Antibody Determination	X		X	X	X	X	
Surgery Data		X					
Hospital Discharge		X					
Postoperative Data			X	X	X	X	X
eurological Status	X		X	X	X	X	X
ostoperative Patient Survey			X	X	X	X	X
Postoperative Oswestry			X	X	X	X	X
SF-36 Questionnaire	X		X	X	X	X	X
Back & Leg Pain Questionnaire	X		X	X	X	X	X
Hip Pain Questionnaire (Control Group Only)		X	X	X	X	X	X
Radiographic Data	X	X	X	X	X	X	X
Adverse Event (if any)		X	X	X	X	X	X
Outstanding AE (if applicable)			X	X	X	X	X
Patient Accountability (If applicable)			X	X	X	X	X
Radiographic Procedures							
Anterior/Posterior *	X	X	X	X	X	X	X
A/P Ferguson (if L5-S1)	X	X	X	X	X	X	X
Lateral X-rays	X	X	X	X			
Lateral Flexion/Extension x-rays	X				X	X	X
CT and/or MRI	X						
CT (high resolution axial, sagittal and coronal reformatting		X			X	X	X**
DEXA Scan***	X						

*If L1-L2, L2-L3, L3-L4, L4-L5 **CT not required past 24 months. ***If one or more parts (a-d) of Exclusion Criteria 6, marked yes.

5.6 Clinical Trial Duration

It is expected that the PMA application for the device will be submitted based on 12 month postoperative results. However, this clinical trial will continue until every enrolled patient has reached 24 months following surgery. Patients are to be evaluated annually after 24 months until every patient in the clinical trial has reached 24 months following surgery. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

5.7 Study Hypotheses and Statistical Considerations

Please refer to the Statistical Considerations section for detailed information regarding study hypotheses and proposed statistical methods, including interim analyses.

6.0 Other Clinical Trial Procedures

6.1 Selection of Investigators

Investigators selected to participate in this clinical trial are responsible for fulfilling the requirements of the protocol and investigators agreement. The following criteria are used to select investigators:

1. Experience and expertise in the use of this type of implant.

2. Sufficient patient population to meet clinical trial expectations.

3. Willingness to comply with the protocol, regulatory requirements, and FDA regulations. Regulatory requirements include the signed investigator agreement and the statements disclosing the financial

relationship investigators might have with Medtronic Sofamor Danek.

4. Ability to complete data in an accurate and timely manner. This includes designating a coordinator with sufficient capabilities and time to assist with the clinical trial.

5. Access to necessary facilities (e.g. radiographs, CT scans, clinical laboratory).

6.2 Investigator Responsibilities

The principal investigator in this clinical trial has specific responsibilities concerning its conduct. These responsibilities include the following:

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

2. Obtaining and maintaining Institutional Review Board (IRB) approval and following their institution's applicable IRB regulations (e.g., submitting reports in a timely manner.)

3. Protecting the rights, safety and welfare of the patients.

4. Obtaining pre-operative written informed consent.

5. Control of the devices under investigation.

6. Fulfilling reporting obligations.

7. Maintaining accurate, complete and current records relating to the investigator's participation in the clinical trial.

8. Allowing the FDA to inspect and copy any records pertaining to the investigation.

6.3 Co-investigator Responsibility

When applicable, a co-investigator participates in the clinical trial under the supervision and guidance of the principle investigator. The co-investigator is also responsible for the terms set forth in the investigator agreement and Clinical Investigational Plan.

6.4 Investigator Records and Reporting Responsibilities

The investigator/coordinator will be supplied study files and patient binders to maintain the records associated with this clinical trial. The investigator is responsible for the following records: correspondence; patient medical records; informed consent documentation; IRB approvals and correspondence; records of device receipt, usage, and disposition; deviations from the protocol; and the signed investigator agreement and financial disclosure.

The investigator is also responsible for specific reporting requirements. These requirements are outlined in the table below.

Report	Submit To	Description
Case Report Forms	Sponsor	Forward to sponsor within 6 weeks of visit.
Unanticipated Device Related Adverse Events	Sponsor and IRB	Report within 10 working days of learning of the event.
Deviations from Investigational Plan	Sponsor and IRB	Any deviation to protect the life or physical well being of a patient in an emergency. Report within 5 working days of the occurrence.
Failure to Obtain Informed Consent	Sponsor and IRB	Report within 5 working days of the occurrence.
Withdrawal of IRB approval	Sponsor	Report within 5 working days of notice.
Annual Progress Report	Sponsor and IRB	Submit annually. Forward written confirmation from IRB of approval to Sponsor.
Final Report	Sponsor and IRB	Submit within 3 months after termination or completion of investigation or investigator's part of investigation.

6.5 IRB Records

Each reviewing IRB should maintain the following records. Record retention requirements described in Section 6.5.

- Clinical Investigational Plan
- Approval application
- Draft and final stamped consent documents
- Meeting minutes
- Investigator progress reports
- Reporting of adverse events according to IRB by-laws
- Correspondence
- Membership Roster
- Written polices and procedures
- Sponsor Interim and Final Reports

6.6 Records Retention and Inspection

Records must be retained at each clinical site and at Medtronic Sofamor Danek for a period of 2 years after the date the study is completed or terminated, or until records are no longer needed to support a regulatory submission. All study records may be subject to regulatory inspection. Contact Medtronic Sofamor Danek for any questions recording record retention.

6.7 Sponsor Records

Medtronic Sofamor Danek will maintain and follow CFR 21 part 812.140 (b).

6.8 Sponsor Reporting Responsibilities

Medtronic Sofamor Danek will maintain and follow CFR 21 part 812.150 (b).

6.9 Training

Training of the investigation team (investigator and staff) will be the responsibility of Medtronic Sofamor Danek clinical personnel and/or regional monitor. Training will occur prior to study initiation at each site. To assure compliance with the Clinical Investigational Plan, training will address the following topics:

- Responsibilities of the investigational team
- Study organization and site responsibilities
- Patient eligibility criteria
- Informed consent procedure

- Storage preparation and use of investigational device
- Data collection requirements and procedures
- Adverse event reporting
- Monitoring and site visit procedures
- Reporting and record keeping
- Regulatory requirements
- Product supply and device accountability

Medtronic Sofamor Danek will document completion of study center preparation and training.

6.10 Patient Recruitment, Informed Consent, and Randomization Processes

1. The patient will be evaluated for enrollment eligibility per the inclusion/exclusion criteria (if an additional MRI, CT, DEXA, or radiographs are required to evaluate the patient for participation in the clinical trial, please have the patient complete the informed consent prior to the procedure).

2. Upon determining eligibility, the patient will be presented information about the clinical trial and asked if he/she would like to participate. If yes, the patient signs the informed consent form.

3. After signing the informed consent form, the patient is assigned a sequential clinical trial number from the investigational site's list of clinical trial numbers. The numbers are used for patient identification and randomization.

The informed consent form and the patient eligibility case report form for a patient who signed the informed consent form and did not subsequently meet the entrance criteria will be maintained. If this occurs, the patient will not be followed for clinical trial purposes after this. This would happen in situations where a MRI, CT, or DEXA scan was needed solely for clinical trial entrance determinations, informed consent form was signed prior to the tests as mentioned in number 1, and the patient subsequently did not qualify for the clinical trial based on the results of the tests.

4. Patients will be randomized according to a randomization schedule generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher. Treatment randomization will be 1:1 (investigational:control) on a site basis.

Both the investigator and the patient will be blinded to the randomization until the patient is admitted to the clinical trial and is assigned an identification number. Upon ensuring that the informed consent form has been property completed, the investigator or designee will open the envelope that corresponds to the patient's assigned clinical trial number to determine if the patient will be randomized into the investigational or control group. The patient and surgeon will not be blinded following the opening of the treatment envelope.

For any patient who refuses treatment after learning of the randomization, the informed consent and preoperative data should be maintained and the reason for refusal of treatment should be documented. All patients that sign an informed consent will be documented and reported to FDA. However, only patients who proceed to surgery and receive the assigned treatment will be counted in the total number of allowed study patients and will be evaluated in the analyses of the data.

The patient informed consent must be approved by the sponsor and IRB. The original signed consent form must be kept in the patient folder at the site and a copy sent to the sponsor. A copy of the signed consent should also be provided to the patient or to his/her legal representative.

6.11 Patient Accountability

Patient follow-up is crucial to the outcome of the clinical trial. Patients should be informed of the importance of returning for follow-up visits and should be evaluated, per inclusion criteria #8, as to their ability and willingness to return for follow-up evaluations. Patients are allowed to withdraw from the study at any time. However, if a patient chooses to do so, this should be documented on the Patient Accountability case report form.

The investigational site should attempt to contact (e.g. telephone, certified mail) patients who do not return for follow-up evaluations. If attempts to contact the patient fail, the site should complete the Patient Accountability CRF and forward to the sponsor.

6.12 Source Documents

All Case Report Form (CRFs) information should be traceable to source documents. Surveys completed by the patient will be considered source documents. Other records that will be considered source documents are the hospital records and clinic charts. Copies of source documents that should be sent to Medtronic Sofamor Danek will include the following: signed and dated patient informed consent documents and operative and discharge summaries. Other source documents may include any relevant notes pertaining to adverse events, reoperations, death, and autopsy reports.

6.13 Protocol Deviations and Changes

A protocol deviation is a non-minor deviation from the Clinical Investigational Plan requirements (i.e., failure to obtained informed consent, failure to meet inclusion/exclusion criteria, etc.). Deviations from the clinical investigational plan (CIP) to protect the life or physical well-being of a subject in an emergency should be reported to the IRB and sponsor no later than 5 working days after the emergency occurred. A minor observation is a failure to comply with the requirements of the Clinical Investigational Plan which is insignificant to the rights, safety and welfare of the patients and/or the scientific soundness of the study and conclusions arising from it. These observations do not constitute a protocol deviation. Minor observations will be reported by the sponsor, Medtronic Sofamor Danek, to FDA and participating investigators and IRBs on an annual basis.

No changes to this protocol will be made without prior written consent from Medtronic Sofamor Danek.

6.13 Implant Preparation and Storage

6.13.1 rhBMP-2 Kit

The rhBMP-2/CRM is supplied in a kit that is packaged in two separate parts. One kit will be needed for the investigational treatment level. One package contains the following components:

<u>2.0 mg/ml Concentration Kit</u>

- Eight vials each containing 6 mg sterile rhBMP-2
- Two vials Sterile Water for Injection (10mL)

- Two 3mL syringe
- Two 5mL syringe
- Four 20-G 1 ½" needles
- One 'Instructions for Preparation'

The second package contains the 20cc sterile Compression Resistant Matrix (CRM).

To prepare the rhBMP-2/CRM device, see the Instructions for Preparation, Attachment IV.A.2.a, and refer to the instructions for preparation which are included in the rhBMP-2/CRM kit supplied by Medtronic Sofamor Danek. Instructions for Preparation are also included with the Surgical Technique.

6.13.2 rhBMP-2/CRM Storage Requirements

The rhBMP-2/CRM components must be stored in a secured location. The rhBMP-2 part of the kit must be maintained under refrigeration (2-8°C) during storage at the investigational site. The CRM component is to be stored at room temperature.

6.13.3 CD HORIZON® Spinal System

The CD HORIZON® Spinal System does not require refrigeration but must be sterilized prior to its use.

6.14 Implantation Procedure

In order to reduce the potential for technique variations which could possibly impact the results, proposed surgical procedures for the investigational implant are provided in the Surgical Technique section.

The procedure for preparing the rhBMP-2/CRM is detailed in the Instruction for Preparation section.

In control patients, the same surgical procedure will be used. Autograft bone from the patient's iliac crest will be placed between the transverse processes.

The surgical procedures for the CD HORIZON® Spinal System are provided in Attachment IV.A.2.c.

Any significant modification to the surgical procedure should be noted in the "Comments" section of the Hospital Discharge case report form.

6.15 Postoperative Regimen

A recommended postoperative regimen for the investigators and their patients is as follows:

1. Wear external orthosis (i.e., corset or brace) for ambulation approximately 6 weeks following surgery.

2. Begin abdominal strengthening program after 30 days following surgery. This should include isometric exercises to strengthen the rectus abdominus muscles, including trunk flexion in the supine position against a resistance so gross flexion does not occur but muscles are stimulated.

3. Patients that are smokers should be encouraged not to smoke.

4. Avoid repetitive bending, stooping, or lifting until fusion occurs or until it has been determined that fusion will not occur.

5. Avoid athletic activities until fusion occurs or until it has been determined that fusion will not occur.

6. Avoid prolonged use of nonsteroidal anti-inflammatory and steroidal drugs. Low dose aspirin for prophylactic anticoagulation is acceptable.

7. Do not use electrical bone growth stimulation for treatment of the lumbar spine during the 24 month follow-up period.

Investigators should follow this surgical procedure and postoperative regimen as closely as possible, unless, in the opinion of the investigator, the patient's clinical condition would be adversely affected by following the surgical procedure or postoperative regimen. Any significant modification of the surgical procedure and/or postoperative regimen will be noted on the appropriate case report form (i.e., "Hospital Discharge-Comments" and/or "Postoperative Data-Comments").

Women who are pregnant will be excluded. In the event that a patient who has received the rhBMP-2/CRM becomes pregnant within one year after implantation of the product, the following actions will be taken:

- The patient will be reminded that the potential risks of exposure to the unborn fetus to components of the rhBMP-2/CRM are unknown.

- The patient and attending obstetric or neonatal physician will be requested to inform the investigator of any adverse experiences relating to the pregnancy. Any adverse experiences will be documented and evaluated as to their potential relationship with the rhBMP-2/CRM.

6.16 Device Explant and Return Procedure

Any rhBMP-2/CRM component that is explanted during a second surgery should be returned for analysis according to the procedures outlined in

Attachment IV.A.5. A copy of the findings will be provided to the investigator after analysis.

Any CD HORIZON® Spinal System component that is explanted in an elective removal will not be returned to the sponsor for evaluation. Any component of the CD HORIZON® system that is explanted in a non-elective removal due to problems with the device, i.e., implant breakage, will be returned to the sponsor for analyses.

6.17 Quality Control Procedures

This section describes the procedures to assure the study is conducted, recorded, and reported in accordance with the CIP, Medtronic Sofamor Danek Work Instructions, Good Clinical Practice, and 21 CRF 812.

6.17.1 Internal Monitoring

Monitoring will be performed by Medtronic Sofamor Danek internal clinical staff and/or representatives through frequent communication with the study site and on-site monitoring.

Data entry will be performed upon receipt of the CRFs to enable follow-up scheduling reports, data validation, discrepancy resolution procedures, and adverse event tracking. Corrections will be made to the database as issues are identified and resolved.

CRFs will be reviewed by qualified clinical staff for completeness, compliance to requirements, and appropriateness of adverse event classification.

Sites may be required to provide copies of source documents to Medtronic Sofamor Danek as noted in Section 6.6, Source Documents. Source documents must be available for regulatory review by Medtronic Sofamor Danek and/or the FDA. Each site will

maintain records of communications with Medtronic clinical staff on study progress, discrepancy resolutions, or any other issues needing resolution.

6.17.2 Clinical Trial Monitoring

The conduct of the clinical trial will be in compliance with applicable sections of 21 CFR 812.

The clinical monitoring for this trial will be conducted by Medtronic Sofamor Danek or a qualified designee (may be a contract research organization). The names and addresses of designated monitor representatives are provided in Section IV.H.

Prior to the enrollment of the first patient at each clinical site, a pre-investigation visit with the Investigator and the study staff will be conducted to review the protocol, case report forms, the procedure for obtaining informed consent, reporting of adverse events, and the procedure for product preparation.

A site-monitoring visit will be conducted during the enrollment period (within the first five patients) so that potential problems can be corrected. Periodic site visits will be based on site performance and will occur at least annually. During the periodic site visits compliance with the protocol may be reviewed as well as device accountability, IRB, and regulatory requirements. Study files, patient CRF folders, and patient clinic and hospital records may also be reviewed.

6.17.3 Initiation Visit

The purpose of the visit is to implement and train the Investigator and the clinical staff on the Clinical Investigational Plan and the

following study elements: IRB/EC requirements, regulatory requirements, device accountability, storage information, case report forms, informed consent procedure, financial disclosure, radiograph requirements, lab guidelines, and data collection procedures. In addition, Medtronic Sofamor Danek representative(s) may also meet with the following departments: radiology, lab, operating room, IRB/EC and pharmacy.

6.17.4 Interim Visit(s)

The purpose of interim visits is to monitor the study. During the periodic site visits, compliance with the protocol may be reviewed as well as adherence to protocol, adequacy of facilities, records maintenance, change in personnel, training of new personnel, informed consent, adherence to data collection schedules, unresolved data discrepancy issues, device accountability, IRB, and regulatory requirements. Study files, patient CRF folders, and patient clinic and hospital records may also be reviewed.

6.17.5 Annual Site Visit

Annual site visits will not be required in addition to the interim visits due the frequency of the interim visits as stated in Section 6.9.2 Clinical Trial Monitoring.

6.17.6 Final Site Visit

A final visit to the center may be made as necessary at the study conclusion or center participation. Any ongoing responsibilities will be discussed with the investigator and the study center coordinator.

6.18 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be formed to oversee the progress and the accumulation of the clinical investigation data. A description of the DSMB for this investigation and its operational procedures are as follows:

6.18.1 Composition of DSMB

The multidisciplinary membership of the DSMB for this clinical investigation will include: two physicians who are not study investigators, and a biostatistician or epidemiologist. The members should be ethically and scientifically supportive of the study objectives and design. In order to assure freedom from apparent significant conflicts of interest, these three board members will not be Medtronic Sofamor Danek employees, will not have a royalty arrangement with Medtronic Sofamor Danek, and do not own or control, directly or indirectly, more than $50,000 worth of Medtronic, Inc. stock. The members will be compensated for their activities associated with the DSMB. Compensation will be based upon an agreed hourly consultation rate plus any incurred expenses.

A confidentiality agreement will be executed with each DSMB member. This agreement will also summarize the expected activities of the DSMB, the compensation, and financial disclosures related to Medtronic Sofamor Danek. Copies of executed agreements and curriculum vitae will be maintained in the IDE files for this study at Medtronic Sofamor Danek.

6.18.2 DSMB Procedures

a. DSMB members will receive a copy of the final investigational plan for their files.

b. DSMB will evaluate the results of the study on a periodic basis. They may be asked to make recommendations concerning the early filing of a PMA application and/or the early stopping of patient enrollment. Any DSMB recommendation to the sponsor will represent a consensus.

The DSMB also will provide a justification for its recommendation.

c. Based on the confidentiality of the investigation and the resulting data, DSMB members cannot disseminate any information regarding the investigation, the results, or its findings and recommendations to any person other than Medtronic Sofamor Danek. Medtronic Sofamor Danek will provide the FDA and reviewing IRB's with copies of DSMB recommendations.